IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant(s)	:	Pasternak et al.
Serial No.	:	09/975,812
For	:	TOPICAL ANESTHETIC/OPIOID FORMULATIONS AND USES THEREOF
Filed	:	October 11, 2001
Examiner	:	Bahar
Art Unit	:	1617

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Charles B. Jackson

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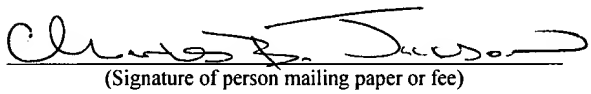

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DECLARATION OF DR. SANDRA C. ROERIG UNDER 37 C.F.R. § 1.132

I declare as follows:

1. I am an associate editor of the editorial board of the Journal of Pharmacology and Experimental Therapeutics. I am familiar with U.S. Application Serial No. 09/975,812. I have been informed that U.S. Application Serial No. 09/975,812 was filed on October 11, 2001, claiming priority to 09/844,111, filed on April 27, 2001 and U.S. Provisional Application Serial No. 60/200,437, filed April 28, 2000. My curriculum vite is provided under Tab 1. I respectfully submit that I am qualified to speak and render opinions as to the

disclosure in the present application, the state of the art and the procedures of editorial review at the Journal of Pharmacology and Experimental Therapeutics. Furthermore, I have reviewed the experimental work discussed herein, in the ordinary course of business.

2. I am familiar with the Office Action dated February 26, 2003, issued by the United States Patent and Trademark Office in connection with the present application and make this Declaration in response thereto. I will address the following issue to respond to the Examiner's rejections:

> The role of peripheral mechanisms in the mediation of antinociceptive responses was unknown prior to the teaching of the present invention. Opioid analgesia was thought to be mediated through the central nervous system (i.e. systemically) rather than through peripheral opioid receptors. Those skilled in the art did not appreciate the significance of peripheral opioid receptor stimulation, much less the significance of combining opioid analgesics and local anesthetics at these peripheral sites. The synergistic potentiation of pain relief that occurs at peripheral sites when opioid analgesics are administered together with local anesthetics was unexpected, especially given that only small amounts of each drug are needed to produce a synergistic response.

3. Details of the editorial review process are described herein. The Journal of Pharmacology and Experimental Therapeutics invites for review original papers dealing with interactions of chemicals with biological systems. All aspects of pharmacology and therapeutics are appropriate. The American Society for Pharmacology and Experimental Therapeutics, which the journal is a member of, requires authors to affirm that original studies reported in the journals of the Society have been carried out in accordance with the Declaration of Helsinki and/or with the Guide for the Care and Use of Laboratory Animals as adopted and promulgated by the U.S. National Institutes of Health.

4. At least two independent reviewers, skilled in the art, are selected for each submitted manuscript. The review is blinded such that the two selected reviewers are unaware of each

other. Comments to the author are intended to be constructive without indicating acceptability of the manuscript. Based substantially on the reviewers' comments, the Associate Editor makes a decision to accept or deny the manuscript for publication. A copy of the reviewers' comments for authors Drs. Yuri Kolesnikov, Igor Chershnev, and Gavril W. Pasternak in response to the manuscript entitled "Analgesic Synergy between Topical Lidocaine and Topical Opioids", is provided under Tab 2. A copy of the manuscript in its published form is provided under Tab 3. To the best of my knowledge, the data reviewed and described in the publication is the same as in the present application.

5. The present invention is directed to topical administration of morphine and lidocaine, which together produce a synergistic antinociceptive response in the periphery. The position of our reviewers was that the synergistic effect of topical morphine and lidocaine at the amounts used was "profound" and "quite marked." Essentially, their position was that the result was unexpected. In addition, one of the reviewers noted that studies of this kind had "never been performed previously." These statements, dated May 19, 2000, provide evidence of the state of the art, from those skilled in the art, at the time the instant application was filed.
6. I further declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and, that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful statements may jeopardize the validity of the application or any patent issued thereon.

Dated 5/12/03

By: Sandra C Roerig
Sandra C. Roerig

Memorial Sloan-Kettering Cancer Center
INVENTION DISCLOSURE FORM

File No. SK901
(File No. completed by Office of Industrial Affairs)

This form is provided to help organize your thoughts about your invention. Be careful to describe what, specifically, makes your invention different from what has been invented before. Avoid general statements that your invention is "Better" - why is it better, or what makes it better?
Descriptive Title of Invention:

2) ***Description of Invention:***

Topical treatments of pain by combination of local anesthetics, opioids, alpha-adrenergic and imidozoline receptors agonists

a) **State as fully as possible, what the invention is**, including:

The demonstration of utility of topical combination of local anesthetics, clonidine, agmatine and opioids for the relief of acute and peripheral neuropathy without systemic absorption and ability of clonidine and agmatine synergistically potentiate of lidocaine analgesia in this paradigm, as well as clonidine and agmatine utility alone as analgesics.

This invention is a(n): _____process _____chemical compound __x__therapeutic method
_____electronic circuit _____mixture of chemical compounds _____apparatus
_____other_____

The problem which this invention solves is:

The significance of this invention lies in its applicability in large variety of painful condition in human. Thus, the analgesic efficacy of topically applied local anesthetics and opioids may be dramatically improved by the addition of clonidine or agmatine. Many of the side –effects of local anesthetics and opioids, such as respiratory depression, constipation, cardio- and neurotoxicity, could be avoided by delivering a drug directly to the site of the pain without significant systemic absorption.

The closest prior art is: (* Please attach copies of relevant publications.)

g) **This invention differs from the closest prior art in that:**

It provides a topical approach, which may limit systemic toxicities and side effects

h) **This invention provides the following advantages:**

i) **This invention possesses the following disadvantages or limitations** (*describe how they can be overcome if applicable*).

j) **Has the invention or any project derived therefrom been:**
1. *Described in a printed publication.* NO____ Date_____
2. *Described in an oral presentation.* NO____ Date_____
3. *Sold, offered for sale, or used in public?* NO___ Date_____
4. *Are any of 1 through 3 contemplated in the near future and, if so, when?*

(*If the answer to any of 1 through 4 is YES, provide detailed information, including copies of manuscripts, published articles, abstracts, etc., together with a floppy disk containing the text of any of your manuscripts, papers or abstracts, etc. that describe the invention. Please indicate the word processing software, version and system [e.g., Wordperfect 5.1,6.1,7 0 or MSWord 7.0 ; RTF; or TXT; IBM].*)

3) **NCI Core Grant No. 08748.** Other Grant(s)/Contract(s) (VERY IMPORTANT IF APPLICABLE):

Sponsor_ NIH_ Award No._____DA00405-01_____

Principal Investigator: Dr.Yuri Kolesnikov

4) **Lab/Department where developed:**

Laboratory of Molecular Neuropharmacology

Contractual Agreem nts with Other Parties (*include name of person contacted and copies of pertinent agreements*):

6) **Who contributed t the invention or discovery?** *Please identify all colleagues who could merit co-authorship credit for the associated publication:*

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Name Home Address	Ext. Dept. Phone No. ( ) Citizenship

(*Include additional names along with the above information on a separate sheet.*)

SIGNATURE OF INVENTOR(S):	SIGNATURES OF WITNESS(ES):
I Da Date , 19	Y. Kol Date , 19